

Folate supplementation during the preconception period, pregnancy and puerperium

Polish Society of Gynecologists and Obstetricians Guidelines

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The proper supply of folate during the preconception period, pregnancy and lactation largely determines the proper development and growth of the fetus and newborn infant. Folate is among the most essential elements of fast-dividing cells as it plays an important role in DNA synthesis. An increased demand for folate, which is not synthesized in the human body, during pregnancy can be met only partially by the supply of foods rich in folate — about 150–250 µg [1]. Folate deficiency is associated with a higher risk of neural tube defects in the fetus, as well as cleft lip and palate and Down syndrome [2]. Disorders of folate metabolism can lead to hyperhomocysteinemia and more frequent complications of pregnancy, such as recurrent miscarriage, intrauterine growth restriction (IUGR) and pre-eclampsia [3, 4].

FOLATE SUPPLEMENTATION

Randomized and cohort studies conducted in the 1980s and 1990s show that folic acid supplementation significantly reduces the risk of neural tube defects [5–12]. The follow-up observations also indicate that folate supplementation reduces the occurrence of heart defects, urinary tract defects, limb defects, cleft lip and palate and pre-eclampsia [3, 4, 13–15].

Recent studies have shown that 12-week supplementation is necessary in the preconception period to achieve adequate red blood cell folate concentration [16, 17].

Folic acid consumed in the form of vitamin supplements must undergo a number of biochemical reactions to reach its active form — 5-methyltetrahydrofolate. Vitamin B12 is

one of the important cofactors of these changes. Vitamin B12 deficiency is particularly unfavourable with high folate concentrations [18]. The resulting disorders in the conversion of homocysteine to methionine lead to hyperhomocysteinemia, which increases the risk of pregnancy complications. Unmetabolized folic acid in the blood can have a negative effect on the human body, as it may affect the activity of natural killer cells and the immune system [19]. Accumulation of unmetabolized folic acid can be avoided by supplementation with appropriate doses and active folate forms. High doses of folic acid may increase the risk of fetal damage in early pregnancy, as well as obesity, insulin resistance and type 2 diabetes in the later life of the offspring [20]. The supplementation dose should be determined based on factors that increase the risk of folate deficiency and fetal defects. The preparations used should also contain vitamin B12.

Recommendations

- All women of childbearing age should include in their diet foods rich in folate (lettuce, spinach, cabbage, broccoli, whole grains, liver, eggs, nuts and cheeses) and fortified foods. (Level B)
- When planning a pregnancy, women of childbearing age should additionally use folate supplementation for at least 12 weeks before conception. (Level B)
- Women should continue to use folate supplementation throughout their pregnancy, puerperium and lactation period. They should use preparations with documented composition and action. (Level D)

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RECOMMENDED DOSES OF FOLATE SUPPLEMENTATION DURING THE PRECONCEPTION PERIOD, PREGNANCY AND LACTATION (TABLE 1)

A group at low risk of fetal defects and pregnancy complications

Randomized, cohort and observational studies have shown a reduction in the risk of neural tube defects in women taking a daily supplement containing 0.4 to 0.8 mg of folic acid. According to the principle of using the lowest effective dose, women who are not at risk of folate metabolism disorders are recommended to take 0.4 mg of folic acid during the preconception period, pregnancy and lactation.

Recommendation

Women in the low-risk group are recommended to take supplements containing 0.4 mg of folate per day. (Level B)

A group at increased risk of fetal defects and pregnancy complications

The occurrence of fetal defects, IUGR and preeclampsia in the previous pregnancy, may indicate an increased risk of

folate deficiency or folate metabolism disorders. This group of women is recommended to take a double dose of folic acid including active forms of folate.

Frequent occurrence of defects in the nervous system has also been observed in fetuses of women with type 1 and type 2 diabetes [21]. It seems that both hyperglycemia and insulin resistance may interfere with folate metabolism. Cohort analysis has indicated a lower percentage of neural tube defects in women with pre-gestational diabetes mellitus taking supplements containing more than 0.4 mg of folic acid [21]. Special attention should be paid to women with polycystic ovary syndrome using metformin. It has been reported that deficiency of folate and vitamin B12 during metformin therapy results in elevated homocysteine levels [22].

Folate deficiency and an increased risk of neural tube defects may be associated with chronic gastrointestinal diseases (colitis ulcerosa, coeliac disease, Crohn's disease) that interfere with absorption. Vitamin deficiencies, including folate deficiency, also occur in women after bariatric surgery [23].

Spina bifida also occurs more frequently in obese women. Studies on folic acid supplementation in this group of

Table 1. Recommended doses in individual groups at risk of fetal defects

Low-risk group	Increased-risk group	High-risk group
0.4 mg/day within 12 weeks before planned pregnancy, during pregnancy and lactation	0.8 mg/day including active folate and vitamin B12 within 12 weeks before planned pregnancy, during pregnancy and lactation	5 mg/day including active folate and vitamin B12 within 12 weeks before planned pregnancy and in the first trimester of pregnancy 0.8 mg/day in the second and third trimesters and during lactation
Healthy women without their own and family history of fetal defects	Fetal defects in the patient's or the closest family history	Neural tube defects in the mother, father or their offspring
	IUGR or/and preeclampsia in the history	
	Pre-gestational diabetes type 1 or 2	
	Digestive diseases: Colitis ulcerosa Crohn's disease Coeliac disease	
	Hepatic failure	
	Renal failure — dialysis	
	Condition after bariatric surgery	
	Obesity	
	Drugs: Anti-epileptics Metformin Methotrexate Cholestyramine Sulfasalazine	
	Stimulants: Smoking Alcoholism	
	Decreased MTHFR activity	

women show lower efficacy of routine supplementation in a group with BMI greater than 24 and a significantly lower risk of spina bifida in children of obese women with high levels of red cell folate [24, 25].

Antiepileptic drug therapy is a risk factor for reduced serum levels of folate in women and supplementation with folic acid during the preconception period may have a beneficial effect on reducing the risk of deficiency. However, the use of high doses, especially above 5 mg, is unreasonable and may lead to a reduction in seizure threshold [26].

Impaired folic acid metabolism and impaired remethylation of homocysteine to methionine, resulting in increased homocysteine levels and decreased plasma folate levels, may be due to reduced methyltetrahydrofolate reductase (MTHFR) activity [27]. There are over 40 types of MTHFR polymorphisms, the most common of which are C677T, A1298C and G1793A. MTHFR 677 C > T is the most common and the best described of them; its frequency varies according to population: in Asian population, the frequency of homozygous dominant individuals ranges from 10% to 15% and heterozygous dominant individuals is up to 50%; in Europe, the frequency of homozygous dominant individuals ranges from 8% to 18%, and in Poland, it is from 5% to 11% [27]. This results in a protein with reduced enzymatic activity — about 70% for homozygous genotypes TT and about 40% for heterozygous genotypes CT. The results of studies conducted in non-pregnant female carriers of different MTHFR genotypes have shown that active forms of folate have increased plasma folate concentrations significantly more than folic acid [28]. Increased supply of folate in pregnancy can mask vitamin B12 deficiency and at the same time increase metabolic disorders leading to hyperhomocysteinaemia [18]. Therefore, it is recommended that supplementation with particularly higher folate doses be supplemented with vitamin B12.

Recommendation

Women in the increased-risk group are recommended to take supplements containing 0.4 mg of folate per day and an additional 0.4 mg, preferably of active folate, per day. Supplements additionally enriched with vitamin B12 are recommended. (Level C)

A group at high risk of fetal defects and pregnancy complications

Neural tube defects may be related to genetic disorders of folate metabolism and chromosomal abnormalities. Research results confirm that the use of folic acid supplementation before pregnancy reduces the risk of reoccurrence by up to 85% [29]. Unfortunately, only 35% of women in whose offspring a neural tube defect reoccurred took preparations

containing folate [30]. Currently there are no studies confirming that empirically recommended high doses of folate are effective. However, due to the high risk of defects, most panel experts recommend doses of 4 to 5 mg during the preconception period and the first trimester of pregnancy. Considering the possibility of negative effects of high doses of folate on the fetus in the next trimesters of pregnancy, the dose should be reduced to 0.8 mg after the first trimester of pregnancy and continued until the end of lactation.

Recommendation

Women in the high-risk group are recommended to take 5 mg of folate per day including active forms of folate and vitamin B12 during the preconception period and the first trimester of pregnancy. The dose of folate should be reduced to 0.8 mg per day during the next trimesters of pregnancy and lactation. (Level D)

Table 2. Recommendations of the Polish Society of Gynaecologists and Obstetricians (PTGP): Folate supplementation during the preconception period, pregnancy and puerperium

1. All women of childbearing age should include in their diet foods rich in folate (lettuce, spinach, cabbage, broccoli, whole grains, liver, eggs, nuts and cheeses) and fortified foods. (Level B)
2. When planning a pregnancy, women of childbearing age should additionally use folate supplementation for at least 12 weeks before conception. (Level B)
3. Women should continue to use folate supplementation throughout their pregnancy, puerperium and lactation period. They should use preparations with documented composition and action. (Level D)
4. Women in the low-risk group are recommended to take supplements containing 0.4 mg of folate per day (Level B).
5. Women in the increased-risk group are recommended to take supplements containing 0.4 mg of folate per day and an additional 0.4 mg, preferably of active folate, per day. Supplements additionally enriched with vitamin B12 are recommended (Level C).
6. Women in the high-risk group are recommended to take 5 mg of folate per day including active forms of folate and vitamin B12 during the preconception period and the first trimester of pregnancy. The dose of folate should be reduced to 0.8 mg per day during the next trimesters of pregnancy and lactation (Level D).

Table 3. Strength of recommendations

- Level A** — recommendations are based on evidence obtained from randomized, controlled trials
- Level B** — recommendations are based on evidence obtained from controlled trials without randomization
- Level C** — recommendations are based on evidence obtained from cohort or case-control analytic studies and from multiple time series with or without the intervention
- Level D** — recommendations are based on expert committee reports or opinions or clinical experience of respected authorities

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